

WEST

Generate Collection

L6: Entry 36 of 38

File: JPAB

Jun 6, 1995

PUB-NO: JP407145081A

DOCUMENT-IDENTIFIER: JP 07145081 A

TITLE: PREPARATION FOR EXTERNAL APPLICATION OF ANTISEPTIC AGENT AND/OR AGENT FOR PROMOTING HEALING OF WOUND

PUBN-DATE: June 6, 1995

INVENTOR-INFORMATION:

NAME

COUNTRY

RUECKERT, DIETER

GUEMBEL, HERMANN

FLEISCHER, WOLFGANG

KAREN, REIMER

WINKLER, HORST

ASSIGNEE-INFORMATION:

NAME

COUNTRY

EURO CELTIQUE SA

N/A

APPL-NO: JP06196903

APPL-DATE: August 22, 1994

INT-CL (IPC): A61K 45/00; A61K 9/06; A61K 9/127; A61K 31/015; A61K 31/05; A61K 31/055; A61K 31/085; A61K 31/305; A61K 31/415; A61K 31/44; A61K 31/455; A61K 31/51; A61K 31/525; A61K 31/79; A61K 33/18

ABSTRACT:

PURPOSE: To obtain a readily applicable preparation for external application of an antiseptic agent and/or an agent for promoting the healing of wounds, containing a liposome preparation and capable of sustaining release and topical actions of an active agent.

CONSTITUTION: This preparation for external application contains a liposome preparation obtained by sealing most of at least one of an antiseptic agent (e.g. povidone-iodine) and/or an agent for promoting the healing of wounds (e.g. allantoin) in the interior of the liposome as an active ingredient. The liposome has a uniform size of about 20 to about 20,000 nm, most preferably about 1,000 nm. The preparation can be formulated into a form such as a solution, a dispersion, a lotion, a cream, an ointment or a gel. When the liposome preparation especially contains the povidone-iodine, the preparation is effective against infectious diseases in the front of eyes, e.g. viral conjunctivitis.

COPYRIGHT: (C)1995, JPO

WEST

Generate Collection

L5: Entry 28 of 34

File: USPT

Aug 13, 1991

DOCUMENT-IDENTIFIER: US 5038769 A

TITLE: Method and apparatus for treating ailments

BSPR:

For most adults, a cold is merely a nuisance. Sometimes it requires a day or two of bed rest, but more often it affects the victim with severe discomfort exemplified by a tired achey feeling. Children, however, often run a fever--and one adult cold virus, known as respiratory syncytial virus, can cause severe illness and even death in infants. Colds can also threaten adults suffering from chronic asthma and bronchitis.

BSPR:

The leading povidone-iodine agent is sold under the trademark "Betadine" and this was the formulation used in the development of one aspect of this invention. Povidone-iodine is a highly effective, broad spectrum topical microbicide for antiseptic use on skin, wounds and mucosa. It is employed widely in the hospital, clinic, office and home. Povidone-iodine differs physically and chemically from all other typical antiseptics and iodophors and is recognized as the only non-detergent iodophor presenting properties different from those of other germicidal iodine compounds or solubilized iodine mixtures. Povidone-iodine provides the following advantages: microbicidal activity, not merely bacteriostatic; broad spectrum microbicidal activity to kill both gram-positive and gram-negative bacteria (including antibiotic-resistant strains), tubercle bacillus, fungi, viruses, protozoa and yeasts; fast acting killing of most pathogens (except spores) within one minute in vitro with many organisms killed in only 15 to 30 seconds; microbicidal activity is maintained in the presence of blood, pus, serum and mucosal secretions; and virtually nonirritating and nonstinging to skin and mucus.

BSPR:

Various prior art devices have been proposed for the treatment of respiratory or infectious problems. The Stuart device, U.S. Pat. No. 1,239,634, produces a flow of warmed air to the patient but not at hyperthermia levels. However, the Stuart device will not be effective against colds as the amount of heat produced is virtually unregulated and not sufficiently high enough. This differs substantially from the invention disclosed herein which produces controlled heated air to take advantage of the properties of hyperthermia. The Stuart device, using the disclosed filter, produces a very unmeasured amount of medicant as there is no way of controlling how much medicant is released from the medicated cotton over a given period of time.

WEST

Generat Collection

L5: Entry 20 of 34

File: USPT

Sep 10, 1996

DOCUMENT-IDENTIFIER: US 5554361 A

TITLE: Processed product for skin and hair treatment

BSPR:

Additionally, it has been found that vitamin A can aid in treatment of many eye disorders (including prevention of night blindness and formation of visual purple in the eye), in helping form and maintain healthy mucous membranes (as well as healthy skin and hair), in building resistance to respiratory infections, and in treating acne, impetigo, boils, carbuncles, and open ulcers when applied externally. Questions have also been raised and some evidence suggested that other benefits of vitamin A could include controlling glaucoma, buffering against cancer, guarding as a part of a bodily, internal defense mechanism against effects of smog and pollution or other environmental toxicity, cushioning against stress, enhancing and speeding healing, helping in removing age spots, fighting infections, fighting skin diseases and shortening the duration of some illnesses.

BSPR:

The Knutson '651 patent reference discloses a wound-healing skin composition containing povidone-iodine, comprising an antimicrobial ointment constituting an admixture of 20 parts by weight of ordinary granulated sugar, 5 parts by weight Betadine.RTM. ointment and 2 parts by weight of Betadine.RTM. solution.

BSPV:

Vitamin A (retinol): helps maintain skin, eyes, urinary tract; and lining of the nervous, respiratory and digestive systems; and is needed for healthy bones and teeth; and that

WEST

Generate Collection

L1: Entry 30 of 68

File: USPT

Oct 11, 1994

DOCUMENT-IDENTIFIER: US 5354934 A

TITLE: Pulmonary administration of erythropoietin

DEPR:

Devices capable of depositing aerosolized EPO formulations in the alveoli of a patient include nebulizers, metered dose inhalers, and powder inhalers. Other devices suitable for directing the pulmonary administration of EPO are also known in the art. All such devices require the use of formulations suitable for the dispensing of EPO in an aerosol. Such aerosols can be comprised of either solutions (both aqueous and non-aqueous) or solid particles. Nebulizers are useful in producing aerosols from solutions, while metered dose inhalers, dry powder inhalers, etc. are effective in generating small particle aerosols. Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to the usual diluents, adjuvants and/or carriers useful in EPO therapy. EPO formulations which can be utilized in the most common types of pulmonary dispensing devices to practice this invention are now described.

WEST

Gen rate Collection

L1: Entry 12 of 68

File: USPT

Jun 1, 1999

DOCUMENT-IDENTIFIER: US 5908611 A

TITLE: Treatment of viscous mucous-associated diseases

BSPR:

The therapeutic composition can be administered to the respiratory airways in the form of an aerosol using a nebulizer, a small particle aerosol generator or an inhaler with propellants. Alternatively, one can instill a therapeutic composition by lavage.

BSPR:

The apparatus can include a nebulizer, a small particle aerosol generator or an inhaler with propellant as the means to deliver the therapeutic composition.

DEPR:

Means for delivering a therapeutic composition comprises a device which produces an aerosol of a liquid composition, which devices are generally well known in the art. These devices can be nebulizers, small particle aerosol generators, inhalers with a propellant, and the like devices.

DEPR:

Alternatively, a small particle aerosol generator, such as the commercially available SPAG-2 or Viratek, generates smaller droplets which are deposited more distally in the airways, such as in the ducts and sacs.

CLPR:

16. The method of claim 1 wherein said aerosol administering comprises contacting said respiratory airway with said composition using a small particle aerosol generator.

WEST

Generate Collection

L1: Entry 31 of 68

File: USPT

Mar 1, 1994

DOCUMENT-IDENTIFIER: US 5290540 A

TITLE: Method for treating infectious respiratory diseases

BSPR:

Currently there is no licensed therapy for PIV3 or Ad-5 lower respiratory disease and the licensed therapy for treating diseases caused by other respiratory viruses is of limited efficacy. In the case of respiratory syncytial virus (RSV), treatment requires the delivery of ribavirin

(1-beta-D-ribofuranosyl-1,2,4,-triazole-3-carboxamide) by small particle aerosol for 12-20 hours a day for at least 3 days (Hall et al., 1983 New Eng. J. Med. 308:1443-1447; Taber et al., 1983 Pediatrics 72:613-618). This treatment involves intervention in the replicative cycle of the RSV. Ribavirin appears to be of only marginal efficacy, and its use has recently come under increasing criticism (Khan, 1991 Am. Rev. Resp. Dis. 143:A510).

BSPR:

It is, therefore, an object of the present invention to provide a therapeutic device, comprising means for delivering directly into the lower respiratory tract of a subject afflicted with disease caused by PIV3, Ad-5, or other infectious agents, an effective amount of a corticosteroid or an anti-inflammatory drug in the form of small particle aerosol, so that said disease or symptoms thereof are either alleviated, controlled, or cured.

DEPR:

The above and various other objects and advantages of the present invention are achieved by (1) a therapeutic device, comprising means for delivering directly into the lower respiratory tract of a subject afflicted with disease caused by PIV3, Ad-5, or other infectious agents, an effective amount of a corticosteroid or other anti-inflammatory drug such as ibuprofen or indomethacin, in the form of small particle aerosol, so that said disease or symptoms thereof are either alleviated, controlled, or cured; and (2) a method of treating respiratory disease, comprising topically administering to a host suffering from pulmonary disease caused by infectious agents such as parainfluenza virus type 3 (PIV3) or adenovirus type 5 (Ad-5), an effective amount of a corticosteroid or a non-steroidal anti-inflammatory drug to produce therapeutic effect against pulmonary disease.

DEPR:

One embodiment of the invention provides a device comprising a therapeutic means that delivers directly into the lower respiratory tract of a host susceptible to or suffering from a lower respiratory tract disease caused by an infectious agent, an amount of an anti-infectious agent and an anti-inflammatory agent effective to produce a therapeutic effect against said disease. This device may have a means comprising a small particle aerosol.

DEPR:

The term "small particle aerosol" as used herein means particles of pharmaceutically acceptable vehicle less than 10 microns in size, preferably less than 5 microns in size, and more preferably less than 2 microns in size containing the drug(s) to be delivered to the lower respiratory tract.

DEPR:

Topical administration was accomplished by anesthetizing the animals, holding them in a vertical posture, and instilling a solution containing corticosteroid onto the nares. A total volume of 0.1 ml/100 gm body weight was used. Previous studies showed that this method of instillation resulted in the rapid deposition

of inoculum into the lungs (Prince et al., 1978, Am. J. Pathol. 93:771-792). A small-particle ultrasonic nebulizer (Portasonic 8500D, DeVilbiss Co., Somerset, PA) was used to demonstrate the feasibility of generating an aerosol of hydrocortisone acetate solution. However, for human administration it is desirable to use a small particle aerosol delivered by a device that could be triggered by inhalation or used synchronously with the inhalation phase of ventilation for patients on a ventilator. Such a device could deliver aerosol from powder (spinaler) or liquid. Since many patients, especially young infants and debilitated adults, may have diminished respiratory inhalation vigor, it is important to synchronize aerosol generation with inhalation. This could be accomplished by having inhalation trigger the aerosol delivery to the airway (nasal prongs, oral tube, etc.). The trigger mechanism could include negative pressure from inhalation, chest movement, or electrical triggering synchronized with diaphragmatic contraction. Electrical leads used to monitor respirations could be used to synchronize aerosol generation to be triggered at the first initiation of diaphragmatic contraction and respiration. Any form of aerosol generator is suitable if aerosol delivery is synchronized with inhalation and appropriate particle size is consistently generated.

CLPR:

1. A method of treating pneumonia in a host, susceptible to or suffering from pneumonia caused by a microorganism selected from a virus, a bacterium, a fungus, and *Pneumocystis carinii*, comprising administering directly into the lower respiratory tract of the host an anti-inflammatory agent selected from a corticosteroid, indomethacin, ibuprofen, and acetylsalicylic acid at a dosage of from 0.1 .mu.g to 1000 mg/kg body weight of the host to reduce inflammation and an anti-infectious agent with activity against said microorganism at a dosage of from 0.1 .mu.g to 1000 mg/kg body weight of the host to reduce the concentration of said microorganism; the anti-inflammatory agent and the anti-infectious agent being administered in the form of a small particle aerosol having a size less than 10 microns.

CLPR:

17. A method of treating pneumonia in a human, susceptible to or suffering from pneumonia caused by respiratory syncytial virus or parainfluenza virus type 3, comprising administering directly into the lower respiratory tract of the human an anti-inflammatory agent selected from a corticosteroid, indomethacin, ibuprofen, and acetylsalicylic acid at a dosage of from 0.1 .mu.g to 1000 mg/kg body weight of the host to reduce inflammation and an human immunoglobulin G at a dosage of from 0.1 .mu.g to 100 mg/kg body weight of the host to reduce the concentration of the respiratory syncytial virus or parainfluenza virus type 3, the anti-inflammatory agent and the anti-infectious agent being administered in the form of a small particle aerosol having a size less than 10 microns.

CLPR:

19. A method of treating pneumonia in a host, susceptible to or suffering from pneumonia caused by parainfluenza virus type 3, adenovirus type 5, or respiratory syncytial virus, comprising administering directly into the lower respiratory tract of the host an anti-inflammatory agent selected from a corticosteroid, indomethacin, ibuprofen, and acetylsalicylic acid at a dosage of from 0.1 .mu.g to 1000 mg/kg body weight of the host to reduce inflammation and an anti-infectious agent with activity against said virus at a dosage of from 0.1 .mu.g to 1000 mg/kg body weight of the host to reduce the concentration of said virus, the anti-inflammatory agent and the anti-infectious agent being administered in the form of a small particle aerosol having a size less than 10 microns.

CLPR:

22. A method of treating pneumonia in a host, susceptible to or suffering from pneumonia caused by a microorganism selected from a virus, a bacterium, a fungus, and *Pneumocystis carinii*, comprising topically administering directly into the lower respiratory tract of the host an anti-inflammatory agent selected from a corticosteroid, indomethacin, ibuprofen, and acetylsalicylic acid at a dosage of from 0.1 82 g to 1000 mg/kg body weight of the host to reduce inflammation and an human immunoglobulin G at a dosage of from 0.1 .mu.g to 100 mg/kg body weight of the host to reduce the concentration of said microorganism, the anti-inflammatory agent and the human immunoglobulin G being administered in the form of a small particle aerosol having a size less than 10 microns.

WEST

Generate Collection

L1: Entry 35 of 68

File: USPT

Sep 17, 1991

DOCUMENT-IDENTIFIER: US 5049389 A

TITLE: Novel liposome composition for the treatment of interstitial lung diseases

PCPR:

Previously disclosed (EP 87309854.5) small particle aerosol liposomes and liposome-drug combinations for medical use tried to circumvent but fell short of the strict size requirement for delivery of steroid into alveoli. With aerosol particle size requirement for deposition in alveoli around 1-2.1 μ m. MMAD, the size of aerosol droplet delivering drug into alveoli must be substantially within that size limit, preferably with the majority of single aerosol droplet about or smaller than 2 μ m. for optimal alveolar deposition. The above cited reference attempted processing a heterogeneous size (1-10 μ m.) population of liposomes into a more homogenous size of small liposomes using an aerosol nebulizer equipped to reduce the size of liposomes. In this manner, the majority of resulting aerosol particles were less than 5 μ m. in diameter with an aerodynamic mass median diameter ranging from about 1-3 microns. Although some of these particles may reach alveoli, a sizable fraction is far too large to be able to enter the small alveoli and consequently, the drug payload in deep lung could be therapeutically insignificant. Also, because of the sizing by aerosolization, the size distribution of these liposomes is unpredictable and the amount of drug deposited in the deep lung cannot be even estimated, not to say predicted, with any degree of certainty.

DEPR:

Since interstitial lung diseases are primarily diseases of the deep lung, the delivery of corticosteroids and other drugs used for treatment of alveolar inflammation to the site of the inflammation is of primary interest. Focused administration of steroids or other drugs to the lung parenchyma via oral inhalation represents an attractive alternative to the oral route for the treatment of ILD and offers the potential to concentrate the drug at a site where it is needed while minimizing systemic absorption and accompanying side effects. Solubilization of steroids in an aqueous formulation and subsequent generation of small aerosol droplets by nebulization are important prerequisites toward achieving this goal. Several inhalation dosage forms of steroid drugs have been previously developed for the treatment of bronchial asthma. However, due to their inherent insolubility, steroid preparations could only be formulated as propellant suspensions, such as for example Freon 11-clathrate suspended in Freon 12/114 mixture or as aqueous suspensions with surfactants. These suspensions, which are administered by nebulization or by using propellant-based meter dose inhalation systems, are not amenable to the generation of small particle aerosols of the type required for deep lung penetration. As has been shown in the parent application, Ser. No. 284,158, filed on Dec. 14, 1988, steroids may be advantageously formulated in nonconventional i.e., nonphospholipid liposomes. Similarly, steroids may be formulated in surfactant micellar solutions. Steroids solubilized in either of these entities are able to be nebulized using appropriate nebulizers to form small particles with good drug output as described above. Nonconventional liposomes offer several advantages including greater loading efficiencies and safety. For example, nonconventional cholesterol sulfate liposome are able to incorporate around 2 mg or more of drug per ml of solution used for nebulization, generating aerosol droplets with a mass median diameter between 0.4-0.9 μ m.. Since the size of the aerosol droplets reaching alveoli is assumed to have MMAD 0.02-2.1 μ m., the aerosol droplets generated by the method described below, are able to be deposited, upon inhalation, in the deep lung of alveolar tissue.

WEST

Generate Collection

L1: Entry 36 of 68

File: USPT

Sep 17, 1991

DOCUMENT-IDENTIFIER: US 5049388 A

TITLE: Small particle aerosol liposome and liposome-drug combinations for medical use

ABPL:

Disclosed are aqueous aerosol droplets containing liposome or interacted liposome-drug or medication combination particles in a continuous phase of air or oxygen-enriched air advantageous for the treatment of a wide variety of diseases. The drug or medication is interacted with the liposome membrane so that on its rupture the drug or medication is not lost from the liposome. Different methods of preparation of the aerosol particles containing the liposome and interacted liposome-drug combination particles are described which can be used in small particle aerosol treatment. The majority of the aerosol droplets containing the liposome particles alone or with drugs has a diameter less than 5 microns and has an aerodynamic mass median diameter ranging from about 1 to 3 microns, and the liposome and interacted-liposome drug particles are substantially uniform in size and less than 1 micron in diameter.

BSPR:

The field of the invention is small particle aerosol liposomes and liposome-drug combinations advantageous for medical use.

BSPR:

Small particle aerosol is defined as a colloid system in which the continuous phase is a gas, and the majority of particles are less than 5 microns in diameter with an aerodynamic mass median diameter ranging from 1 to 3 microns. The advantage of such a discretely sized population of particles is that, because of their small size and low settling velocities, they will penetrate when inhaled into the lower respiratory tract in substantial percentages. For example, 1.5 micron particles will deposit 46 percent of the total inhaled dose in the lung and another 36 percent in nose and upper air passages. Such uniform deposition will permit treatment of lesions at any level of the respiratory tract (Gilbert, B. E., Wilson, S. Z., and Knight, V., 1986, Ribavirin Aerosol Treatment of Influenza Virus Infections. In: Options for the Control of Influenza. UCLA Symposium on Molecular and Cellular Biology. Alan R. Liss, Inc., New York, N.Y., p. 343.)

BSPR:

Small particle aerosol treatment delivers a high dose of drug to the epithelium of the respiratory tract in amounts largely unachievable by other routes of administration (Knight, V. 1973, Airborne Transmission and Pulmonary Deposition of Respiratory Viruses. In: Viral and Mycoplasmal Infections of the Respiratory Tract. V. Knight, ed. Lea and Febiger, Philadelphia, Pa., p. 1). There is a subsequent steady rate of absorption of drug into the systemic circulation.

BSPR:

The present invention is directed to small particle aqueous aerosol droplets containing liposomes and interacted drug-liposome combinations propelled in air or oxygen-enriched air having advantageous properties for medical use. Small particle aerosol, as used herein, is a colloid system in which the continuous phase is air or oxygen-enriched air, and the majority of aerosol particles is less than 5 microns in diameter with an aerodynamic mass median diameter ranging from 1 to 3 microns. Before aerosolization the liposomes are heterogeneous in size ranging from less than 1 micron up to 10 microns in diameter. Advantageously, the particle size of the liposomes and the liposome-drug particles are substantially homogenized by the aerosol nebulizer to sizes of less

than one micron in diameter. Most particles are much less than 1 .mu.m in diameter and several may be included in the aqueous particles generated by the aerosol generator. These smaller liposome and liposome-drug particles retain their pharmacological activity.

BSPR:

Small particle aerosol treatment containing liposomes alone is advantageous since liposomes can closely mimic pulmonary surfactant and may repair defects in this system that have developed for a variety of reasons.

BSPR:

Small particle aerosol treatment with interacted drug liposome particles is advantageous in that, when the liposome permeability barrier is damaged, such as during aerosolization, the drug is not prematurely released from the liposome.

BSPR:

The drugs to be given by liposome-drug combinations range widely as does the dosage. In general, the drugs in recommended dosages for non-aerosol liposome-drug combinations of the prior art can be used for the small particle aerosol liposome-drug combinations without the disadvantages of the prior art liposome-drug combinations. The amount of the drug in the liposome-drug combination aerosol is controlled by the concentration of drug in the reservoir of the aerosol generator. Also, the amount of drug employed depends on the duration of treatment, drug used and the like. For example, dosage for 24 hours can range from less than a nanogram to a few grams depending on need, toxicity, biological and chemical properties of the drug, and other factors. Liposome-drug or medication combinations include those which interact with the liposome membrane so that on rupture of the membrane the drug or medication is not lost from the liposome, referred to herein as lipophilic drugs or medications interacted with the liposome membrane.

DRPR:

FIGS. 1 and 1A are views of two commercially available nebulizers, the Puritan Bennett nebulizer, FIG. 1 being model No. 1920, and FIG. 1A being model No. 1917, useful in generating aqueous small particle aerosol droplets containing liposomes and liposome-drug particles in air or oxygen-enriched air of the invention.

DEPR:

As previously set forth, the present invention is directed to small particle aqueous aerosol particles containing liposomes and interacted drug liposome combination particles propelled or carried in air or oxygen-enriched air to methods of generating aerosols of them, and to methods of treating patients with them. As the term "Small particle aerosol" is used herein, it is defined as a colloid system in which the continuous phase is an air or oxygen-enriched air, and the majority of the aerosol particles or droplets is less than 5 microns in diameter with an aerodynamic mass median diameter ranging from 1 to 3 microns in diameter containing liposomes or liposome drug particles less than 1 micron in diameter. Liposome-drug combinations of the prior art are heterogeneous in size ranging from less than 1 micron up to 10 microns in diameter and have been given to patients in relatively large oral or intravenous doses. Such dosage may result in high plasma concentrations but low concentrations in the respiratory epithelium. Unexpectedly, the heterogeneous liposome particles and the interacted drug liposome combination particles can readily be converted to a more homogeneous small size by an aerosol nebulizer without any loss in effectiveness of the liposomes and interacted drug liposome combination particles while contained in aqueous aerosol particles of the above diameter size while propelled or carried in air or oxygen-enriched air. Advantageously, these small particle aqueous aerosol droplets containing these liposomes and liposome-drug combinations, when inhaled, provide high concentration on the respiratory epithelium and a steady rate of absorption into the circulation without the hazard of peak levels that may be associated with large oral or intravenous doses of drug, and deliver a high dose of drug to the epithelium of the respiratory tract in amounts largely unachievable by other routes of administration. One to several liposomes or liposome-drug particles (<1 micron in diameter) may be contained in a single aerosol droplet (1-3 micron, aerodynamic mass median diameter) depending on the concentration of liposome material in the preparation that is to be nebulized. As previously mentioned, the advantage of such a discretely sized population of particles is that because of their small size and low settling velocities they will penetrate when inhaled into the lower respiratory tract in substantial

percentages. For example, 1.5 micron particles will deposit 46% of the total inhaled in the lung and another 36% in the nose and upper air passages. Such uniform deposition permits treatment of lesions at any level of the respiratory tract and also provides an interface into the cell without the problems and disadvantages associated with oral and intravenous injections.

DEPR:

The following Table 1 describes medications of lipophilic nature which may be interacted with the lipid of liposome and be administered by small particle aerosol.

DEPR:

Any biologically active compound (medication) may be associated with liposomes. Whether the compound is associated with the lipid portion of the liposomes or resides in the aqueous compartments is dependent upon the physical and chemical properties of the compound of biological interest. It is understood that the procedures used for preparing liposome-drug combinations are not restricted under this invention, any procedure that results in liposomes would be applicable. For purposes of disclosure, two general methods of producing interacted drug liposomes are described below. They illustrate that regardless of chemical and physical properties a wide array of biologically active compounds or medications can be interacted with liposomes and that such liposomes are applicable to delivery by small particle aerosol.

DEPR:

FIG. 2 is a photograph of enviroxime-containing liposomes as they were initially made and showing that they are very heterogeneous in size, ranging from 0.7 microns down to less than 0.03 microns in diameter. Following processing by the small particle aerosol generator (SPAG), the liposomes become more homogeneous in size, as shown in FIGS. 3 and 4, with larger ones being less than 0.35 microns in diameter. FIG. 5 is an enlargement of the liposomes of FIGS. 3 and 4 illustrating that they retain their liposomes characteristics and are multi-lamellar liposomes of "classical" structure after generation in a small particle aqueous aerosol.

DEPR:

Liposomes containing 2-4 mg of cyclosporine A prepared by the above procedures were also placed in a Collison small particle aerosol generator and delivery of drug containing liposomes was confirmed in particles ranging from less than 1 micron to greater than 5 microns. The aerodynamic mass median diameter of the aqueous particles in the aerosol was found to be 1.8 to 2.0 microns. This particle size range is similar as observed with other liposome preparations (e.g., enviroxime) and solutions of water soluble drugs (e.g., ribavirin).

DEPR:

The dosage of liposome drug preparations in small particle aerosol administered by inhalation can be controlled at three different points. The first is the concentration of drug in the liposome. This is controlled by the chemical nature of the drug and the lipid of the liposome. Certain ratios of drug-liposome combinations are required to form optimally functioning liposomes. Ratios of such combinations commonly found suitable are 10% to 40% content of drug in the liposome preparation.

DEPR:

Retention by patients of drugs following inhalation in small particle aerosol can be estimated. The basis for estimates includes particle size distribution, density of particles, concentration of drug in particles, age, sex, and other factors (Knight, V., Yu, C. P., Gilbert, B. E., and Divine, G. W. 1988, Estimating the dosage of Ribavirin Aerosol According to Age and Other Variables. Journal Infect. Dis. 158(2):443-448). Liposome-drug aerosols suspended in watery media are aqueous aerosols and their particle size distribution corresponds closely with aqueous aerosols. This is demonstrated in FIGS. 6A and 6B where the particle size distribution of a liposome-enviroxime aerosol was measured from a Collison generator (SPAG-2-6000 model). The liposome-enviroxime preparation consisted of 450 mg of egg yolk lecithin and 120 mg of enviroxime combined in liposomes. This material was suspended in 30 mL of distilled water for use. Thus, the enviroxime concentration was 4 mg/mL. The APS 3300 particle size analyzer (TSI, Inc.) was used to count particles. The sample time was 20 seconds and assumed density of aerosol particles was 1.0 g/cm³. The nebulizer pressure was 26 psi and the flow rate was 7.5 lpm. The drying air flow rate was 5.0 lpm.

Thus, the total flow rate was 12.5 lpm. Four runs were made with the following AMMD particle size: 1.00, 1.15, 1.41, and 0.98 (mean 1.15 microns). The AMMD of the test shown was 1.00 microns. It was found that the aerodynamic mass median diameter (AMMD) approximated 1.0 micron and virtually all particles were less than 5 microns in diameter. This value is similar to that of small particle aqueous aerosols produced by this generator when there are no liposomes present. This measurement was representative of four tests. Because of this close similarity, it is reasonable to use the method of estimation of respiratory tract dosage for aqueous aerosols to estimate dosage of liposome-enviroxime and other similar aerosols.

DEPR:

FIG. 7 shows a nomogram which was derived to estimate aerosol dosage based on the concentration of the drug ribavirin in the aqueous liquid of the aerosol generator. By determining the ratio of the concentration of ribavirin and enviroxime in the aerosol reservoir, the estimated dosage of enviroxime administered in liposomes can be obtained. The ribavirin aerosol contains 20 mg/mL of ribavirin in the liquid reservoir at the beginning of treatment and the enviroxime concentration is 4 mg/mL. Thus, to predict the dose of enviroxime aerosol retained by the patient, the concentration of enviroxime in the reservoir liquid (4 mg/mL) is divided by the concentration of ribavirin in the reservoir liquid (20 mg/mL). The dose of enviroxime retained after inhalation of aerosol would be 20 percent of that of ribavirin retention. Thus, from FIG. 7, a dose of enviroxime for a 25 year old male would be 0.18 mg/hr (0.9 mg/kg/hr of ribavirin retained.times.0.2 ratio of enviroxime concentration to ribavirin concentration).times.70 (weight of patient in Kg) or 12.6 mg retained per hour of treatment. With this methodology, it is possible to estimate the dosage of any drug contained in liposomes administered by small particle aerosol. Table 1 shows a list of drugs which are lipophilic in nature and may be prepared in liposomes and administered in small particle aerosol. The usual dosages of those drugs by other routes is indicated. In general, dosage by liposome aerosol would be appreciably less than that recommended by other routes.

DEPC:

Estimation of dosage of liposome-interacted drugs administered in small particle aerosol

DETL:

TABLE 1 _____ Doses of drugs that interact with liposomes and may be administered in a liposome formulation by small particle aerosol inhalation. Average adult doses for some indications are

given: Cardiac glycosides Digoxin 1.2 to 1.6 mg, loading dose, 0.1 mg daily, maintenance dose Digoxin 8-12 microgram/kg, loading dose, 2.5-4 microgram/kg, maintenance dose Anti-convulsant Tegritol 600-800 mg/day Anti-parasitic Praziquantel 25-60 mg/kg/day for 1-2 days Anti-arrhythmic Isosorbide 2.5-10 mg/dose, repeat according to response Hormones Anti-diuretic (ADH) (Vasopressin) 5 to 60 units/day Cortico steroids Daily Doses Drug Equivalent Dose/Day Cortisone 25 mg-50 mg Hydrocortisone 20 mg-40 mg Prednisolone 5 mg-10 mg Meprednisone 4 mg-8 mg Methylprednisolone 4 mg-8 mg Triamcinolone 4 mg-8 mg Paramethasone Acetate 2 mg-4 mg Dexamethasone 0.750 mg-1.5 mg Betamethasone 0.6 mg-1.2 mg Testosterone 10-25 mg, 3 times/week Estrogen, Natural 1-2 mg/day Thyroxine 1-2 mg/day Androgens 200-400 mg/day Hydroxy progesterone 375 mg every 4 weeks Anti-diabetic Acetohexamide 0.5-1 gm/day Chlorpropamide 100-250 mg/day Tolbutamide 100-250 mg-3.0 gm/day Anti-hormone Bromocriptine mesylate 1.25-2.5 mg/day Immune suppressive Cyclosporine A 500 mg-1000 mg/day Anticancer Uracil mustard 0.10-0.15 mg/kg weekly for 4 weeks Methotrexate Anti-fungal Amphotericin B 50-100 mg/day Ketoconazole 100-200 mg/day Griseofulvin 330-375 mg/day Miconazole 100-200 mg/day Tranquilizers Chlorpromazine 30-75 mg/day Fluphenazine decanoate 5-10 mg/day Reserpine 0.25 mg/day Antihistamines Terfenadine 40-600 mg/day Anti-viral Acyclovir 800-1000 mg/day Azidothymidine 800-1000 mg/day Ganciclovir 800-1000 mg/day Enviroxime 10-20 mg/day Winthrop 51711 20-40 mg/day Anti-malarial Chloroquine phosphate 300 mg/week Vaccines (purified sub-units) Human Immunodeficiency virus Influenza virus 5-20 micrograms/dose Respiratory syncytial virus

DETL:

TABLE 2 _____ Substances which are substantially water soluble that if suitably derivatized so that they interact with lipid of

liposomes can be administered in small particle aerosol

Antiasthma Antiarrhythmic Tranquilizers
metaproterenol propranolol hydroxyzines aminophylline atenolol theophylline
verapamil Antihistamines terbutaline captopril pyribenzamine ephedrine
chlorpheniramine isoproterenol Hormones diphenhydramine adrenalin ACTH
norepinephrine gonadotropin Antihypertensives Antidiabetic Sedatives & Analgesic
apresoline insulin dilaudid atenolol demerol oxymorphone Antiparasitic
pentamidine Anticancer Vaccines azathioprine Hemophilus influenza Antibiotic
bleomycin Pneumococcus penicillin adriamycin tetracycline daunorubicin Antifungal
cephalothin vincristine miconazole cefotaxime carbenicillin Immunotherapies
Antiviral vancomycin interferon ribavirin gentamycin interleukin-2 rimantadine/
tobramycin monoclonal antibodies amantadine piperacillin gammaglobulin moxalactam
Other cefazolin Antihypotension cell surface receptor cefadroxil dopamine
blocking agents cefoxitin dextroamphetamine

WEST[Help](#)[Logout](#)[Interrupt](#)[Main Menu](#)[Search Form](#)[Posting Counts](#)[Show S Numbers](#)[Edit S Numbers](#)[Preferences](#)**Search Results -**

Terms	Documents
small adj1 particle adj1 aerosol	68

Database:

- US Patents Full-Text Database
- US Pre-Grant Publication Full-Text Database
- JPO Abstracts Database
- EPO Abstracts Database
- Derwent World Patents Index
- IBM Technical Disclosure Bulletins

Refine Search:

small adj1 particle adj1 aerosol

[Clear](#)**Search History****Today's Date: 5/8/2001**

<u>DB Name</u>	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u>
USPT,JPAB,EPAB,DWPI,TDBD	small adj1 particle adj1 aerosol	68	<u>L1</u>